(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 December 2001 (27.12.2001)

PCT

(10) International Publication Number
WO 01/97798 A1

(51) International Patent Classification[7]: A61K 31/195

(21) International Application Number: PCT/US01/18632

(22) International Filing Date: 8 June 2001 (08.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/212,148 16 June 2000 (16.06.2000) US
60/223,880 8 August 2000 (08.08.2000) US

(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM CORPORATION** [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BALDONI, John, M.** [US/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US). **KEARNEY, Albert** [US/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US). **ROMAN, Robin, S.** [US/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US).

(74) Agents: **DUSTMAN, Wayne, J.** et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW 2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/97798 A1

(54) Title: METHOD FOR THE PREVENTION OR REDUCTION OF CARDIOVASCULAR EVENTS ASSOCIATED WITH CORONARY INTERVENTION

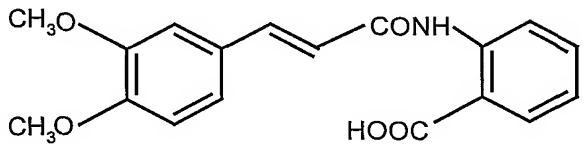
(57) Abstract: This invention provides a method for the prevention or reduction of cardiovascular events associated with coronary intervention in a mammal, particularly a human, which comprises administering to the subject N-(3',4'-dimethoxycinnamoyl)anthranilic acid or a pharmaceutically acceptable salt thereof as a coating on or incorporated n a non-biodegradable or biodegradable stent in association with coronary intervention. Also included in this invention is the co-administration of compounds active in the reduction of cardiovascular events associated with coronary intervention and stents with medicaments thereon or therein, or radioactive stents.

METHOD FOR THE PREVENTION OR REDUCTION OF CARDIOVASCULAR EVENTS ASSOCIATED WITH CORONARY INTERVENTION

Field of Invention

The present invention relates to a method for the prevention or reduction of cardiovascular events associated with coronary intervention.

More particularly, the method comprises administrating to a mammal, particularly a human patient, after coronary intervention a stent, preferably a non-biodegradable (i.e. metallic or polymeric) or a biodegradable stent, coated with or incorporating N-(3',4'-dimethoxycinnamoyl)anthranilic acid (Tranilast) represented by the following formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient.



(I)

BACKGROUND OF THE INVENTION

1. Technical Field of the Invention

Coronary intervention is a percutaneous procedural approach to the treatment of ischemic heart disease such as angina pectoris and myocardial infarction. Coronary intervention technically involves mechanical revascularization of a stenosed lesion in a coronary artery by means of a balloon catheter, stent placement, an atherectomy catheter and the like. As a consequence, coronary intervention often causes restenosis due to damaged intima and media cells. Patients who experience restenosis may require revascularization procedures to correct the condition. Other cardiovascular events associated with coronary intervention include myocardial infarction and death.

Up to the present time, there has not been any effective drug for the prevention or reduction of cardiovascular events associated with coronary intervention.

2. DESCRIPTION OF THE RELATED ART

Tranilast is sold commercially as a drug for the treatment of allergic diseases, e.g., allergic bronchitis, allergic asthma, atopic dermatitis, and the like, based on the activity exhibited by the drug for inhibiting release of chemical mediators [The Journal of Allergy and Clinical Immunology, Vol. 57, No. 5, pp. 396-407, (1976)].

More recently, in Biochemical Pharmacology, Vol. 36, No. 4, pp. 469-474 (1987), it was reported that Tranilast inhibits fibroblast proliferation and collagen accumulation.

United States Patent No. 5,385,935 ('935) claims the use of Tranilast in the inhibition of restenosis associated with coronary intervention but indicates that an oral dosage regimen with a treatment period of at least three consecutive months is required for efficacy. The requirement of a three plus month treatment period was premised, in part, upon a publication in the Japanese College of Cardiology (1988), cited in the '935 patent. This publication discloses the treatment of patients subjected to the PTCA procedure with Tranilast in a daily oral dose of 300 mg for 30 consecutive days after the PTCA procedure. The clinical data obtained from this study did not indicate any significant efficacy for inhibiting a restenosis effect associated with the PTCA procedure at the tested dosage and duration. The '935 patent indicates that the lack of efficacy for inhibiting a restenosis effect with Tranilast after the 30 day protocol was due to a too short duration of treatment.

Conversely, the '935 patent demonstrated that an extended period of Tranilast treatment was effective for lowering the incidence of post-procedure restenosis associated with PTCA. It was found that dosing patients with Tranilast for a duration of at least about three months (i.e., a term of at least about 90 consecutive days of treatment) reduced the incidence of restenosis associated with the PTCA procedure. In one clinical study, when patients were administered Tranilast in a daily oral dose of 600 mg for three consecutive months after the PTCA procedure, the incidence of restenosis was less than about 20%. As reported in the '935 patent, the incidence of restenosis associated with the PTCA procedure usually is about 40%.

Additionally, in Nobuyoshi M. et al., J Am Coll. Cardiol. 1988; 12: 616 to 623, it was observed that most cases of restenosis after successful coronary angioplasty occur within 6 months after the procedure, particularly between 1 and 3 months after coronary angioplasty.

Thus, restenosis is considered to take place predominantly in the healing phase after coronary angioplasty and, using Tranilast, to require at least three months of treatment in order to show a therapeutic effect.

United States Patent No. 5,837,008 ('008), claims a method of delivering a therapeutic substance to the interior of a body lumen. The '008 does not teach or disclose a method using Tranilast.

United States Patent No. 5,733,327 ('327), claims a biodegradable stent containing tranilast. The '327 patent does not teach or disclose a biodegradable stent containing tranilast for use in reducing the cardiovascular events of myocardial infarction, death or the need for revascularization procedures that are associated with coronary intervention.

Numerous advantages would be realized if Tranilast could be efficaciously administered on a stent, preferably a non-biodegradable or a biodegradable stent, for the prevention or reduction of cardiovascular events associated with coronary intervention. The advantages of a coated/incorporated stent over conventional dosing include: elimination of patient compliance as an issue, exposure of the patient to less total medication, reduced side effect profile and providing a more cost effective treatment.

Advantages would also be realized if Tranilast could be administered as a coating on or incorporated within an intravascular stent or as an active ingredient in a biodegradable stent. For example, the known toxic effects of Tranilast would be lessened.

It has now been discovered that Tranilast can be suitably administered in the prevention or reduction of cardiovascular events associated with coronary intervention as a coating on a stent or as an active ingredient in a biodegradable stent.

SUMMARY OF THE INVENTION

This invention relates to a method for the prevention or reduction of cardiovascular events associated with coronary intervention in a mammal, particularly a human, which comprises administering to the subject N-(3',4'-dimethoxycinnamoyl)anthranilic acid or a pharmaceutically acceptable salt thereof as a coating on or incorporated into a non-biodegradable of biodegradable stent.

Other objects, features and advantages of the present invention will become apparent from the following description and examples.

DETAILED DESCRIPTION OF THE INVENTION

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set forth.

Illustrative of acceptable salts for use herein are inorganic salts such as sodium or calcium salt, or organic salts formed with amines such as morpholine, piperidine, arginine, and the like.

As coronary intervention in the present invention, for example, is stent placement or Percutaneous Transluminal Coronary Angioplasty (PTCA), Directional Coronary Atherectomy where stent placement is be included.

By the phrase "cardiovascular events" as used herein, is preferably meant myocardial infarction and death associated with coronary intervention. Also included in the term cardiovascular events is the need for revascularization procedures associated with

coronary intervention. Also included in the term cardiovascular events is the reduction in the occurrence of severity of restenosis. A preferred embodiment of this invention is the reduction in the cardiovascular events of myocardial infarction and/or death and/or the need for revascularization procedures associated with coronary intervention when tranilast is administered as an active ingredient in a biodegradable stent.

By the phrase "prevention or reduction" of cardiovascular events as used herein, is meant that the incidence of myocardial infarction and/or death and/or the need for revascularization procedures and/or restenosis associated with coronary intervention in Trailast treated patients are prevented or reduced in comparison to untreated patients.

By the phrase "the need for revascularization procedures", as used herein, includes the determination that a revascularization procedure is required to restore artery function and/or the actual incidence of revascularization procedures performed.

By the phrase "in association with coronary intervention" as used herein, is meant that the treatment with Tranilast is administerd on the stent used in the coronary intervention procedure or as an active ingredient in a stent.

By the term " collected over the observation period" as used herein, means a period of up to 12 months.

The present invention relates to a method for the prevention or reduction of cardiovascular events associated with coronary intervention in a mammal, particularly a human, which comprises administering to the subject N-(3',4'-dimethoxycinnamoyl)anthranilic acid (Tranilast) or a pharmaceutically acceptable salt thereof as a coating on a stent or as an active ingredient in a biodegradable stent in association with coronary intervention.

A preferred method of use in the current invention is a method for preventing or reducing myocardial infarction associated with coronary intervention.

A preferred method of use in the current invention is a method for preventing or reducing death associated with coronary intervention.

A preferred method of use in the current invention is a method for preventing or reducing the need for revascularization procedures associated with coronary intervention.

The efficacy of the presently invented method is demonstrated by the Examples below.

The present invention therefor provides a method for the prevention or reduction of cardiovascular events associated with coronary intervention in a mammal, particularly a human, which comprises administering to the subject N-(3',4'-dimethoxycinnamoyl)anthranilic acid (Tranilast) or a pharmaceutically acceptable salt thereof as a coating on or incorporated into a non-biodegradable or biodegradable stent.

The invention also provides for the use of Tranilast or a pharmaceutically acceptable salt thereof in the prevention or reduction of cardiovascular events associated with coronary intervention in a mammal, particularly a human, as a coating on or incorporated into a non-biodegradable or biodegradable stent.

The invention also provides for a pharmaceutical composition for use in the prevention or reduction of cardiovascular events associated with coronary intervention in a mammal, particularly a human, which comprises Tranilast or a pharmaceutically acceptable salt thereof as a coating on or incorporated into a non-biodegradable or biodegradable stent.

The invention also provides for a pharmaceutical composition comprising Tranilast, or a pharmaceutically acceptable salt thereof, and a stent.

Also contemplated within the scope of this invention is the co-administration of tranilast or a pharmaceutically acceptable salt thereof as a coating on or incorporated into a non-biodegradable or biodegradable stent and a further active ingredient known to prevent or reduce cardiovascular events associated with coronary intervention. Preferably, the further active ingredient is tranilast. The further active ingredient, preferably tranilast, can be administered orally or parenterally by methods known in the art, such as described in PCT/US00/02622 (which published as International Application WO 00/45811 on August 10, 2000), PCT/US00/02611 (which published as International Application WO 00/45810 on August 10, 2000) or US Patent 5,385,935 - Issued January 31 1995). Advantages of the co-administration of tranilast as a coating on or incorporated into a non-biodegradable or biodegradable stent and a further active ingredient known to prevent or reduce cardiovascular events associated with coronary intervention include: increased efficacy over the administration of either component individually, reduction in the amount of the further active ingredient (preferably tranilast) administered, allowing for a more favorable dosing protocol of the further active ingredient (such as fewer doses taken over a given period of time), reduced toxicity in the combined treatment due to the changes in dosing of the further active ingredient.

Also contemplated within the scope of this invention is the co-administration of a further active ingredient known to prevent or reduce cardiovascular events associated with coronary intervention and a stent with a medicament as a coating on or incorporated into a non-biodegradable or biodegradable stent. Preferably, the further active ingredient is tranilast. Preferably the medicament is selected from tranilast, actinomycin, rapamycin or paclitaxel. These preferred medicaments are well known to those of skill in the art. The medicaments can be incorporated into and/or onto the stent by known means such as described in United States Patent No. 5,733,327 to Igaki et al. and United States Patent No. 5,464,450 to Buscemi et al. Also included in the present combination is a stent which is radioactive. That is the medicament associated with the stent is radioactivity. The further

active ingredient, preferably tranilast, can be administered orally or parenterally by methods known in the art, such as described in PCT/US00/02622 (which published as International Application WO 00/45811 on August 10, 2000), PCT/US00/02611 (which published as International Application WO 00/45810 on August 10, 2000) or US Patent 5,385,935 - Issued January 31 1995). Advantages of the co-administration of a medicament as a coating on or incorporated into a non-biodegradable or biodegradable stent and a further active ingredient known to prevent or reduce cardiovascular events associated with coronary intervention include: increased efficacy over the administration of either component alone, reduction in the amount of the further active ingredient (preferably tranilast) administered, allowing for a more favorable dosing protocol of the further active ingredient (such as fewer doses taken over a given period of time), reduced toxicity in the combined treatment due the changes in dosing of the further active ingredient.

Tranilast is generally described in United States Patent 3,940,422. Tranilast and pharmaceutically acceptable salts and compositions thereof can be readily prepared by known methods such as described in United States Patent 3,940,422.

When Tranilast or a pharmaceutically acceptable salt thereof is employed therapeutically, it can be administered as a coating on incorporated into a non-biodegradable or biodegradable stent by known methods such as descibed in United States Patent No. 5,733,327 to Igaki et al. and United States Patent No. 5,464,450 to Buscemi et al.

Coated stents can be made by methods known to those of skill in the art.

When a pharmaceutical composition of the present invention is employed therapeutically, as a coating on or incorporated into a non-biodegradable or biodegradable stent the exact mode of administration can be changed depending upon the weight and age and sex of the patient, the severity of the condition to be treated, and the like.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the strength of the preparation, the exact mode of administration, and the advancement of the disease condition. Additional factors depending on the particular patient being treated will result in a need to adjust dosages, including patient age, weight, diet, and time of administration.

No unacceptable toxicological effects are expected when compound of the invention is administered in accordance with the present invention.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

EXAMPLE I

Efficacy of the invented method for preventing or reducing incidence of myocardial infarction associated with PCTA surgery is demonstrated by the following.

One hundred forty nine lesions with a partial occlusion, which undergo successful PTCA procedures with smooth dilation, are selected for study. These lesions are divided into two groups, and both groups do not differ significantly with sex, distribution of coronary artery or ratio of lesions restenosed after PTCA; One group (about 49 lesions) receives Tranilast administered on a non-biodegradable stent (hereinafter identified as group I), and another group (about 100 lesions) does not receive Tranilast (hereinafter identified as group II). In addition, patients may also be given a calcium antagonist, nitrates and/or anti-platelet agents.

The comparative clinical data collected over the observation period demonstrate the efficacy of Tranilast treatment administered on a non-biodegradable stent for the prevention or reduction of incidence of myocardial infarction in patients after the PTCA procedure.

EXAMPLE II

Efficacy of the invented method for preventing or reducing incidence of death associated with PCTA surgery is demonstrated by the following.

One hundred forty nine lesions with a partial occlusion, which undergo successful PTCA procedures with smooth dilation, are selected for study. These lesions are divided into two groups, and both groups do not differ significantly with sex, distribution of coronary artery or ratio of lesions restenosed after PTCA; One group (about 49 lesions) receives Tranilast administered as an active ingredient on a biodegradable stent (hereinafter identified as group III), and another group (about 100 lesions) does not receive Tranilast (hereinafter identified as group IV). In addition, patients may also be given a calcium antagonist, nitrates and/or anti-platelet agents.

The comparative clinical data collected over the observation period demonstrate the efficacy of Tranilast treatment administered as an active ingredient on a biodegradable stent for the prevention or reduction of incidence of death in patients after the PTCA procedure.

EXAMPLE III

Efficacy of the invented method for preventing or reducing the need for revascularization procedures associated with PCTA surgery is demonstrated by the following.

One hundred forty nine lesions with a partial occlusion, which undergo successful PTCA procedures with smooth dilation, are selected for study. These lesions are divided into two groups, and both groups do not differ significantly with sex, distribution of coronary artery or ratio of lesions restenosed after PTCA; One group (about 49 lesions) receives Tranilast administered as an active ingredient in a biodegradable stent (hereinafter identified as group V), and another group (about 100 lesions) does not receive Tranilast (hereinafter identified as group VI). In addition, patients may also be given a calcium antagonist, nitrates and/or anti-platelet agents.

The comparative clinical data collected over the observation period demonstrate the efficacy of Tranilast treatment administered as an active ingredient in a biodegradable stent for the prevention or reduction the need for revascularization procedures in patients after the PTCA procedure.

EXAMPLE IV

Efficacy of the invented method for preventing or reducing incidence of myocardial infarction associated with PCTA surgery is demonstrated by the following.

One hundred forty nine lesions with a partial occlusion, which undergo successful PTCA procedures with smooth dilation, are selected for study. These lesions are divided into two groups, and both groups do not differ significantly with sex, distribution of coronary artery or ratio of lesions restenosed after PTCA; One group (about 49 lesions) receives Tranilast administered as a coating in a non-biodegradable a stent (hereinafter identified as group VII), and another group (about 100 lesions) does not receive Tranilast (hereinafter identified as group VIII). In addition, patients may also be given a calcium antagonist, nitrates and/or anti-platelet agents.

The comparative clinical data collected over the observation period demonstrate the efficacy of Tranilast treatment administered as a coating in a non-biodegradable a stent for the prevention or reduction of incidence of myocardial infarction in patients after the PTCA procedure.

EXAMPLE V

Efficacy of the invented method for preventing or reducing incidence of death associated with PCTA surgery is demonstrated by the following.

One hundred forty nine lesions with a partial occlusion, which undergo successful PTCA procedures with smooth dilation, are selected for study. These lesions are divided into two groups, and both groups do not differ significantly with sex, distribution of

coronary artery or ratio of lesions restenosed after PTCA; One group (about 49 lesions) receives Tranilast administered as a coating on a non-biodegradable stent (hereinafter identified as group IX), and another group (about 100 lesions) does not receive Tranilast (hereinafter identified as group X). In addition, patients may also be given a calcium antagonist, nitrates and/or anti-platelet agentss.

The comparative clinical data collected over the observation period demonstrate the efficacy of Tranilast treatment administered as a coating on a non-biodegradable stent for the prevention or reduction of incidence of death in patients after the PTCA procedure.

EXAMPLE VI

Efficacy of the invented method for preventing or reducing the need for revascularization procedures associated with PCTA surgery is demonstrated by the following.

One hundred forty nine lesions with a partial occlusion, which undergo successful PTCA procedures with smooth dilation, are selected for study. These lesions are divided into two groups, and both groups do not differ significantly with sex, distribution of coronary artery or ratio of lesions restenosed after PTCA; One group (about 49 lesions) receives Tranilast administered as an active ingredient in a biodegradable stent (hereinafter identified as group XI), and another group (about 100 lesions) does not receive Tranilast (hereinafter identified as group XII). In addition, patients may also be given a calcium antagonist, nitrates and/or anti-platelet agents.

The comparative clinical data collected over the observation period demonstrate the efficacy of Tranilast treatment administered as an active ingredient in a biodegradable stent for the prevention or reduction the need for revascularization procedures in patients after the PTCA procedure.

EXAMPLE VII

Efficacy of the invented method for preventing or reducing the need for revascularization procedures associated with PCTA surgery is demonstrated by the following.

One hundred forty nine lesions with a partial occlusion, which undergo successful PTCA procedures with smooth dilation, are selected for study. These lesions are divided into two groups, and both groups do not differ significantly with sex, distribution of coronary artery or ratio of lesions restenosed after PTCA; One group (about 49 lesions) receives Tranilast administered as a coating in a non-biodegradable stent (hereinafter

identified as group XIII), and another group (about 100 lesions) does not receive Tranilast (hereinafter identified as group XIV). In addition, patients may also be given a calcium antagonist, nitrates and/or anti-platelet agents.

The comparative clinical data collected over the observation period demonstrate the efficacy of Tranilast treatment administered as a coating in a non-biodegradable stent for the prevention or reduction the need for revascularization procedures in patients after the PTCA procedure.

EXAMPLE VIII

Efficacy of the invented method for preventing or reducing incidence of death associated with PCTA surgery is demonstrated by the following.

One hundred forty nine lesions with a partial occlusion, which undergo successful PTCA procedures with smooth dilation, are selected for study. These lesions are divided into two groups, and both groups do not differ significantly with sex, distribution of coronary artery or ratio of lesions restenosed after PTCA; One group (about 49 lesions) receives Tranilast administered as a coating on a non-biodegradable stent and tranilast administered orally in a daily dose of 600 mg (administered in two 300mg tablets about 12 hours apart) for three consecutive months (hereinafter identified as group XV), and another group (about 100 lesions) does not receive Tranilast (hereinafter identified as group XVI). In addition, patients may also be given a calcium antagonist, nitrates and/or anti-platelet agents.

The comparative clinical data collected over the observation period demonstrate the efficacy of Tranilast treatment co-administered as a coating on a non-biodegradable stent and orally for the prevention or reduction of incidence of death in patients after the PTCA procedure.

EXAMPLE IX

Efficacy of the invented method for preventing or reducing the need for revascularization procedures associated with PCTA surgery is demonstrated by the following.

One hundred forty nine lesions with a partial occlusion, which undergo successful PTCA procedures with smooth dilation, are selected for study. These lesions are divided into two groups, and both groups do not differ significantly with sex, distribution of coronary artery or ratio of lesions restenosed after PTCA; One group (about 49 lesions) receives paclitaxel administered as a coating on a biodegradable stent and tranilast administered orally in a daily dose of 900 mg (administered in two 450mg tablets about 12

hours apart) for one month (hereinafter identified as group XVII), and another group (about 100 lesions) does not receive treatment (hereinafter identified as group XVIII). In addition, patients may also be given a calcium antagonist, nitrates and/or anti-platelet agents.

The comparative clinical data collected over the observation period demonstrate the efficacy of paclitaxel treatment administered as a coating on a biodegradable stent and oral administration of tranilast for the prevention or reduction the need for revascularization procedures in patients after the PTCA procedure.

EXAMPLE X

Efficacy of the invented method for preventing or reducing the need for revascularization procedures associated with PCTA surgery is demonstrated by the following.

One hundred forty nine lesions with a partial occlusion, which undergo successful PTCA procedures with smooth dilation, are selected for study. These lesions are divided into two groups, and both groups do not differ significantly with sex, distribution of coronary artery or ratio of lesions restenosed after PTCA; One group (about 49 lesions) receives rapamycin administered as a coating in a biodegradable stent and tranilast administered orally in a daily dose of 600 mg (administered in two 300mg tablets about 12 hours apart) for one month (hereinafter identified as group XXI), and another group (about 100 lesions) does not receive treatment (hereinafter identified as group XXII). In addition, patients may also be given a calcium antagonist, nitrates and/or anti-platelet agents.

The comparative clinical data collected over the observation period demonstrate the efficacy of rapamycin treatment administered as a coating in a biodegradable stent and oral administration of tranilast for the prevention or reduction the need for revascularization procedures in patients after the PTCA procedure.

EXAMPLE XI

Efficacy of the invented method for preventing or reducing incidence of myocardial infarction associated with PCTA surgery is demonstrated by the following.

One hundred forty nine lesions with a partial occlusion, which undergo successful PTCA procedures with smooth dilation, are selected for study. These lesions are divided into two groups, and both groups do not differ significantly with sex, distribution of coronary artery or ratio of lesions restenosed after PTCA; One group (about 49 lesions) is implanted with a radioactive stent and is administered tranilast orally in a daily dose of 600 mg (administered in two 300mg tablets about 12 hours apart) for one month (hereinafter

identified as group XXIII), and another group (about 100 lesions) does not receive treatment (hereinafter identified as group XXIV). In addition, patients may also be given a calcium antagonist, nitrates and/or anti-platelet agents.

The comparative clinical data collected over the observation period demonstrate the efficacy of treatment via the administration of a radioactive stent and oral administration of tranilast for the prevention or reduction of incidence of myocardial infarction in patients after the PTCA procedure.

While the preferred embodiments of the invention are illustrated by the above, it is to be understood that the invention is not limited to the precise instructions herein disclosed and that the right to all modifications coming within the scope of the following claims is reserved.

What is claimed is:

1. A method for the prevention or reduction of cardiovascular events associated with coronary intervention in a mammal, particularly a human, which comprises administering to the subject N-(3',4'-dimethoxycinnamoyl)anthranilic acid or a pharmaceutically acceptable salt thereof as a coating on a stent.

2. Tranilast coated onto or incorporated into a non-biodegradable stent.

3. A pharmaceutical composition comprising Tranilast, or a pharmaceutically acceptable salt thereof, and a stent.

4. A method for the prevention or reduction of cardiovascular events associated with coronary intervention in a mammal, particularly a human, which comprises administering to the subject N-(3',4'-dimethoxycinnamoyl)anthranilic acid or a pharmaceutically acceptable salt thereof as an active ingredient in or on a biodegradable stent.

5. The method of claim 1 wherein the cardiovascular event is myocardial infarction.

6. The method of claim 4 wherein the cardiovascular event is myocardial infarction.

7. The method of claim 1 wherein the cardiovascular event is death.

8. The method of claim 4 wherein the cardiovascular event is death.

9 The method of claim 1 wherein the cardiovascular event is the need for revascularization procedures.

10 The method of claim 4 wherein the cardiovascular event is the need for revascularization procedures.

11. A method for the prevention or reduction of cardiovascular events associated with coronary intervention in a mammal, particularly a human, which comprises co-

administering to the subject tranilast as a coating on or incorporated into a non-biodegradable or biodegradable stent and a further active ingredient known to prevent or reduce cardiovascular events associated with coronary intervention.

12. The method of claim 11 wherein the further active ingredient is tranilast.

13. A method for the prevention or reduction of cardiovascular events associated with coronary intervention in a mammal, particularly a human, which comprises co-administering to the subject a further active ingredient known to prevent or reduce cardiovascular events associated with coronary intervention and a stent coated with a medicament as a coating on or incorporated into a non-biodegradable or biodegradable stent.

14. The method of claim 13 wherein the further active ingredient is tranilast.

15. The method of claim 13 wherein the medicament is tranilast.

16. The method of claim 13 wherein the medicament is actinomycin.

17. The method of claim 13 wherein the medicament is rapamycin.

18. The method of claim 13 wherein the medicament is paclitaxel.

19. The method of claim 13 wherein the stent is radioactive.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/18632

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/195

US CL : 514/563

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/563

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,046,239 A (LENNOX et al.) 04 April 2000,see the entire document.	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or prior date and not in conflict with the application but cited to understa the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot considered novel or cannot be considered to involve an inventive s when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot considered to involve an inventive step when the document is combi with one or more other such documents, such combination be obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 24 JULY 2001	Date of mailing of the international search report 14 AUG 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ZOHREH FAY Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)★